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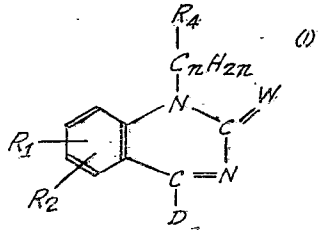
(54) QUINAZOLINE DERIVATIVES AND PROCESSES FOR PRODUCING THEM

(71) We, SUMITOMO CHEMICAL COMPANY LIMITED, of 15, Kitahama-5-chome, Higashi-ku, Osaka, Japan, a corporation organized under the laws of Japan, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

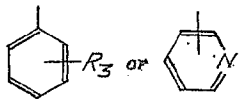
This invention relates to novel quinazoline derivatives and processes for the production thereof.

More particularly, according to the present invention there are provided quinazoline derivatives of the formula,



(I)

wherein D is a group of the formula,



n is 0, 1, 2 or 3; R_1, R_2 and R_3 are each independently a hydrogen or halogen atom, or a nitro, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfinyl or trifluoromethyl group; R_4 is an unsubstituted or C_{1-4} alkyl - substituted C_3—C_6 cycloalkyl group; and W is oxygen or sulfur, and pharmaceutically acceptable acid addition salts thereof.

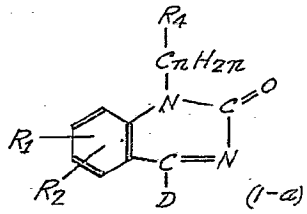
The invention also provides methods of making them and pharmaceutical compositions containing them.

Preferred compounds falling within the general formula (I) have D a phenyl, o - halogenophenyl or 2 - pyridyl; n is 1; R_1 as hydrogen, halogen, methyl methoxy, nitro or trifluoromethyl, R_1 being substituted at the 6 - position of the quinazoline ring; R_2 as hydrogen and R_4 as cyclopropyl.

In the compounds of the formula (I), the halogen atom can be a chlorine, bromine, iodine or fluorine atom; the C_{1-4} alkyl group

can be a methyl, ethyl, n - propyl, isopropyl, n - butyl, isobutyl or tertiary - butyl group, the C_{1-4} alkoxy group can be a methoxy, ethoxy, n - propoxy, isopropoxy, n - butoxy, isobutoxy or tertiary - butoxy groups, and examples of the unsubstituted or C_{1-4} alkyl - substituted C_{3-6} cycloalkyl group are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclopropyl and dimethylcyclopropyl. When the $—C_nH_{2n}—$ group is an alkylene group having 1, 2 or 3 carbon atoms, it may be methylene, ethylene, 1 - methylethylene, 2 - methylethylene or trimethylene.

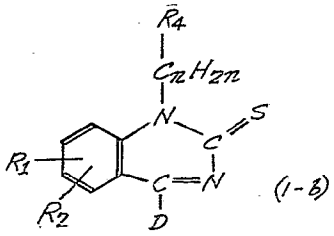
Certain of the compounds falling within the formula (I) are of the formula,



(I-a)

wherein D, n, R_1, R_2 and R_4 are as defined above.

Some other compounds falling within the formula (I) are of the formula,



(I-b)

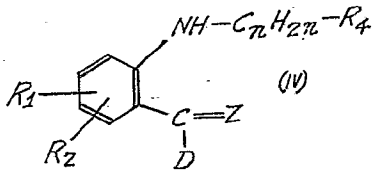
wherein D, n, R_1, R_2 and R_4 are as defined above.

According to the present invention, there is also provided a pharmaceutical composition containing as an active ingredient a quinazoline derivative of the formula (I), given and defined above, or a pharmaceutically acceptable acid addition salt thereof, and a pharmaceutically acceptable carrier.

Compounds within the formula (I) and the pharmaceutically acceptable acid addition salts (e.g. the hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, acetic acid, maleic acid, fumaric acid, tartaric acid, succinic acid or citric acid addition salt) of such compounds have excellent pharmacological properties, especially as anti-inflammatory and analgesic agents, and they are also useful as intermediates for preparing other medicines. Illustratively, 1 - cyclopropylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone shows remarkable inhibitory action against carrageenin - induced edema in rats, and inhibits the edema by 44.8% at 15 mg/kg (per os), 53.3% at 75 mg/kg (per os) and 73.1% at 150 mg/kg (per os), while no toxic symptoms are observed and occult bleeding is negative in the feces after oral administration of 1,500 mg/kg in rats. The anti-inflammatory activity of this compound is found to be 6 - times higher than that of 1,2 - diphenyl - 3,5 - dioxo - 4 - n - butylpyrazolidine (phenylbutazone), and the acute, subacute and chronic toxicities are much lower than those of phenylbutazone.

According to processes within the present invention, the quinazoline derivatives within the formula (I) may be prepared by a variety of methods.

One method for preparing a quinazoline derivative of the formula (I) includes reacting a compound of the formula,



(IV)

wherein R_1, R_2, R_4, D and n are the same as defined above, and Z represents an oxygen atom or an imino group, with a compound having

$$—\overset{|}{N}—\overset{|}{C}=O,$$

$$—\overset{|}{N}—\overset{|}{C}=S,$$

$$—N=C=O$$

or

$$—N=C=S$$

group in the molecule such as cyanic acid or a salt thereof, thiocyanic acid or a salt thereof, a carbamic acid ester, a thiocarbamic acid ester or a carbamic acid halide. Examples of salts of cyanic acid include sodium cyanate, ammonium cyanate and potassium cyanate. Examples of salts of thiocyanic acid include sodium thiocyanate, potassium thiocyanate and ammonium thiocyanate. Examples of carbamic acid esters include alkyl carbamates such as ethyl carbamate and methyl carbamate. An example of a carbamic acid halide is carbamoyl chloride.

The reaction is optionally carried out in the presence of a solvent. The reaction temperature and solvent used vary depending upon which compound having a

$$—\overset{|}{N}—\overset{|}{C}=O,$$

$$—\overset{|}{N}—\overset{|}{C}=S,$$

—N=C=O

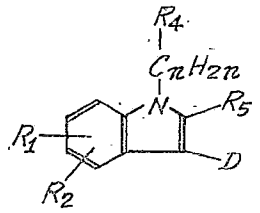
or

—N=C=S

group is used.

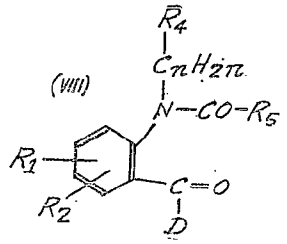
A 2(1H) - quinazolinethione derivative of the formula (I-b) may be converted to the corresponding 2(1H) - quinazolinone derivative of the formula (I-a) on treatment with an oxidizing agent in a solvent or solvent mixture. Examples of the oxidizing agent are hydrogen peroxide and permanganates. The choice of solvent depends on the oxidizing agent. The reaction temperature varies depending upon the oxidizing agent. Also, a the 2(1H) - quinazolinone derivative of the formula (I-a) may be converted to a 2(1H) - quinazolin - thione derivative of the formula (I-b) by reaction with phosphorus pentasulfide.

A compound of the formula (IV) can be obtained by reacting indole derivatives of the formula,



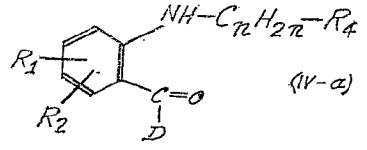
(VII)

wherein D, R_1, R_2, R_4 and n are as defined above, and R_5 is a C_{1-4} alkoxy - carbonyl, carboxy, carbamoyl or cyano group, with an oxidizing agent, and then by hydrolyzing the resultant corresponding compound of the formula,



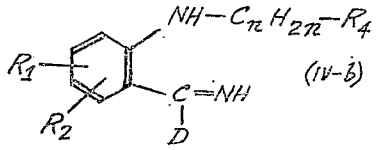
(VIII)

wherein D, R_1, R_2, R_4, R_5 and n are as defined above to yield a compound of the formula,



(IV-a)

wherein R_1, R_2, R_4, D and n are as defined above. This may then optionally be treated with ammonia to yield a compound of the formula,



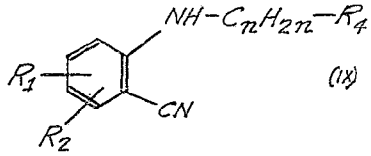
(IV-b)

wherein R_1, R_2, R_4, D and n are as defined above.

Examples of the oxidizing agents used in the oxidation of the indole derivatives of the formula (VII) are ozone, hydrogen peroxide, peracids (e.g., performic, peracetic and perbenzoic acids), chromic acid and potassium permanganate. A preferred oxidizing agent is chromic acid or ozone. The oxidation reaction is preferably effected in the presence of a solvent or solvent mixture. The choice of solvent depends on the oxidizing agent employed, and suitable solvents may include water, acetone, carbon tetrachloride, acetic acid and sulfuric acid. The oxidizing agent is used in at least the stoichiometric amount. The reaction temperature varies depending on the oxidizing agent.

The hydrolysis of the compounds of the formula (VIII) proceeds in the presence of a hydrolyzing agent. Examples of hydrolyzing agents include mineral acids such as hydrogen chloride and sulfuric acid; alkali metal hydroxides such as sodium hydroxide, and potassium hydroxide, alkali earth metal hydroxides such as calcium hydroxide and barium hydroxide, alkali metal carbonates such as sodium carbonate and potassium carbonate, and ammonia derivatives such as ammonium hydroxide. The hydrolysis reaction is preferably carried out in a solvent or solvent mixture. Some examples of suitable solvents are water, methanol, ethanol, acetone and dimethylsulfoxide and their mixtures.

A compound of the formula (IV-b) may also be obtained by treating a benzonitrile derivative of the formula,



(IX)

wherein R_1, R_2, R_4 and n are as defined above, with a compound represented by the formula,

D—M (X)

wherein D is as defined above, and M is Li,

MgBr, MgCl or MgI, in the manner described in Japanese Patent Publication No. 26457/69.

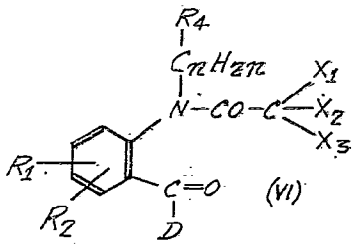
Another method for preparing a quinazoline derivatives of the formula (I) comprises treating a compound of the formula (IV-b) with phosgene, and further optionally treating the resultant product of the formula (I-a) with phosphorus pentasulfide.

The reaction of the compound of the formula (IV-b) with at least an equimolar amount of phosgene is preferably carried out in the presence of an inert solvent such as ether, benzene, chloroform, toluene or dioxane. The reaction is preferably carried out in the presence of an acid-binding agent. Examples of suitable acid-binding agents are tertiary organic bases such as triethylamine, tributylamine, pyridine or N - methylpiperidine; alkali metal hydroxides such as sodium hydroxide or potassium hydroxide; and alkali metal carbonates such as sodium carbonate or potassium carbonate.

A further method for preparing a quinazoline derivatives of the formula (I-a) is described as follows. That is, a compound represented by the formula (IV-a) is reacted with a trihalogenoacetic acid of the formula,

(V)

wherein X_1, X_2 and X_3 are each independently a halogen atom, or a reactive derivative thereof, and the resulting trihalogenoacetamide derivative of the formula,



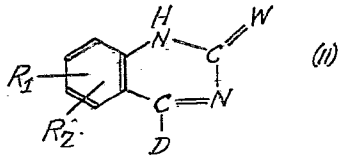
(VI)

wherein R_1, R_2, R_4, D, n, X_1, X_2, and X_3 are as defined above, is then reacted with ammonia.

Examples of the reactive derivative of the trihalogenoacetic acid are acid halides, anhydrides and esters. The reaction may optionally be carried out in the presence of an inert solvent and optionally with a condensing agent. The solvent selected depends upon the trihalogenoacetic acid or reactive derivative thereof employed. Thus, a solvent which is inert to the two starting materials is preferably used. Suitable inert solvents are, for example, benzene, toluene, xylene, ether, tetrahydrofuran, methylene chloride and chloroform. However, when the trihalogenoacetic acid derivative or the condensing agent employed is a liquid, the reaction is preferably carried out in the absence of the solvent. When using acid halides, it is desirable to carry out the reaction in the presence of a condensing agent, which may be an inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate and potassium carbonate, or an organic base such as pyridine or triethylamine. Excess of the compound of the formula (IV-a) may also be used as the base. If a free trihalogenoacetic acid is used, suitable condensing agents are, in particular, dicyclohexylcarbodiimide, N - cyclohexyl - N' - (2 - morpholinoethyl)-carbodiimide or phosphorus trichloride.

The reaction of a trihalogenoacetamido derivative of the formula (VI) thus obtained with ammonia is carried out in the presence of a solvent. An alcohol is desirable as the solvent to be employed for this process. Suitable alcohols include methanol, ethanol, isopropyl alcohol and tertiarybutyl alcohol. Dimethylsulfoxide may also be preferably used. Ammonia is used in at least the stoichiometric amount, and is added to the reaction mixture as gaseous, alcoholic or liquid ammonia or as an ammonium salt which generates ammonia during the reaction (e.g. ammonium acetate or ammonium formate). In general, the reaction proceeds at room temperature, but the temperature may optionally be higher or lower, to effect the desired control of the reaction.

A still further method for preparing a quinazoline derivative of the formula (I) includes reacting a 1 - unsubstituted quinazoline derivative of the formula,



(II)

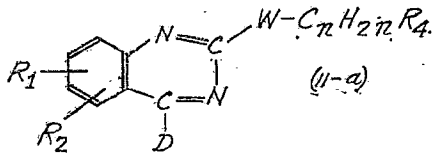
wherein R_1, R_2, D and W are as defined above, with a reactive derivative of a compound represented by the formula,

$$HO—C_nH_{2n}—R_4 \qquad (III)$$

wherein R_4 and n are as defined above. Examples of the reactive derivative are halides such as the chloride, bromide and iodide and sulfonic acid esters such as the methanesulfonate, p - toluenesulfonate, β - naphthalenesulfonate and trichloromethane-

sulfonate. A compound of the formula (II) may be reacted with a reactive derivative of the compound of the formula (III) in the presence of an alkaline agent, or the compound of the formula (II) may be contacted with an alkaline agent to form the metal salt and the resulting metal salt may then be contacted with a reactive derivative of the compound of the formula (III). Examples of the alkaline agents are alkali metal hydrides such as sodium hydride or lithium hydride, alkali metal hydroxides such as potassium hydroxide, alkali metal amides such as sodium amide, potassium amide or lithium amide, alkyl alkali metals such as butyl lithium, phenyl alkali metals such as phenyl lithium and alkali metal alcoholates such as sodium methylate, sodium ethylate and potassium tertiary - butoxide. The reaction may, in general, be effected in an organic solvent or solvent mixture. Suitable solvents are, for example, benzene, toluene, xylene, dimethylformamide, dimethylacetamide, diphenyl ether, diglyme, dimethyl sulfoxide, methyl ethyl ketone and N - methyl - pyrrolidone, and mixtures thereof. The reaction may be carried out at a temperature within a range of from room temperature to the boiling point of the solvent employed inclusively.

The reaction is often accompanied by the formation of the quinazoline derivatives of the formula,



(II-a)

wherein D, n, R_1, R_2, R_4 and W are as defined above. The separation of the desired quinazoline derivatives of the formula (I) from the quinazoline derivatives of the formula (II-a) may be effected in by conventional means, for example by chromatography. When the 1 - unsubstituted quinazoline of the formula (II), wherein W is a sulfur atom, is reacted with a reactive derivative of a compound of the formula (III), the resultant product is mainly a quinazoline derivative of the formula (II-a).

Using these processes, the following quinazoline derivatives can be obtained:

1 - cyclopropylmethyl - 4 - phenyl - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 5 - chloro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 7 - chloro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - bromo - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - fluoro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - chloro - 8 - methyl - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - methoxy - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - methylthio - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - methylsulfonyl - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - trifluoromethyl - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6,8 - dichloro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (*o* - fluorophenyl) - 6 - nitro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (*o* - chlorophenyl) - 6 - nitro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (*m* - chlorophenyl) - 6 - nitro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (*p* - chlorophenyl) - 6 - nitro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (*o* - tolyl) - 6 - nitro - 2(1H) - quinazolinone
1 - cyclopropylethyl - 4 - phenyl - 6 - nitro - 2(1H) - quinazolinone
1 - cyclopropylpropyl - 4 - phenyl - 6 - nitro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - nitro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - methylsulfinyl - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6,7 - dichloro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - chloro - 8 - nitro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - chloro - 8 - methylthio - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6,7 - dimethyl - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6,7 - dimethoxy - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinethione
1 - cyclopropylmethyl - 4 - (*p* - methoxyphenyl) - 6 - chloro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (*o* - chlorophenyl) - 6 - chloro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (*p* - chlorophenyl) - 6 - chloro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (*m* - chlorophenyl) - 6 - chloro - 2(1H) - quinazolinone

1 - cyclopropylmethyl - 4 - (*m* - chlorophenyl) - 6 - methoxy - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (*o* - fluorophenyl) - 6 - chloro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (*p* - fluorophenyl) - 6 - chloro - 2(1H) - quinazolinone
1 - cyclopropylethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (2′ - pyridyl) - 6 - chloro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (2′ - pyridyl) - 6 - bromo - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (3′ - pyridyl) - 6 - chloro - 2(1H) - quinazolinone
1 - cyclopropylmethyl - 4 - (4′ - pyridyl) - 6 - chloro - 2(1H) - quinazolinone
1 - cyclobutylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone
1 - cyclopentylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone
1 - cyclohexylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone
1 - cyclohexyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone
1 - cyclohexylethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone

Processes within the present invention and intermediate steps of such processes are further described in the following Examples of more preferred embodiments thereof, which are presented for the purpose of illustration and do not limit the scope of the invention.

Example 1

A solution of 50 g. of chromic anhydride in 50 ml. of water is added dropwise to a suspension of 60.2 g. of ethyl 1 - cyclopropylmethyl - 3 - phenyl - 5 - chloroindole - 2 - carboxylate in 340 ml. of glacial acetic acid at 20°—25°C. The mixture is heated at 50°—55°C. for 6 hours. The reaction mixture is poured into water and extracted with toluene. The toluene extracts are combined, washed with water and dried over sodium sulfate, and the solvent is removed under reduced pressure to give 61.8 g. of crude 2 - (N - cyclopropylmethyl - ethoxalyl-amino) - 5 - chlorobenzophenone as an oil. Crystallization from ethanol - petroleum ether gives colourless crystals having a melting point of 67—68°C.

The crude 2 - (N - cyclopropylmethyl-ethoxalyl - amino) - 5 - chlorobenzophenone. Thus obtained is dissolved in 260 ml. of dimethyl sulfoxide. To the solution is added 57 g. of 40% aqueous potassium hydroxide solution, and the mixture is heated at 50°—55°C. for 2 hours. The reaction mixture is diluted with water and the deposited precipitates are collected by filtration, washed with water and dried to give 43.4 g. of crude 2 - cyclopropylmethylamino - 5 - chlorobenzophenone having a melting point of 77°—78°C. Recrystallization from ethanol gives the pure product having a melting point of 86°—87°C.

Example 2

A mixture of 25 ml. of concentrated hydrochloric acid and 25 ml. of water is added to a solution of 2.5 g. of 2 - (N - cyclopropylmethylethoxalyl - amino) - 5 - chlorobenzophenone in 62.5 ml. of ethanol. The mixture is heated under reflux for 6 hours. After cooling, the reaction mixture is concentrated under reduced pressure, diluted with 100 ml. of water and extracted with chloroform. The chloroform extracts are combined, washed successively with water and with 20% potassium hydroxide solution, and dried over sodium sulfate. The chloroform is removed under reduced pressure to give 2 - cyclopropylmethylamino - 5 - chlorobenzophenone quantitatively.

Example 3

Using a procedure similar to that described in Example 1, but replacing ethyl 1 - cyclopropylmethyl - 3 - phenyl - 5 - chloroindole - 2 - carboxylate by 1 - cyclopropylmethyl - 3 - phenyl - 5 - chloro - indole - 2 - carboxylic acid, the compound 2 - (N - cyclopropylmethylhydroxyoxalyl - amino) - 5 - chlorobenzophenone is obtained as an oil.

A mixture of 8 g. of 2 - (N - cyclopropylmethylhydroxyoxalyl - amino) - 5 - chlorobenzophenone, 9.2 g. of sodium hydroxide and 100 ml. of water is refluxed for 2 hours. The reaction mixture is cooled and the precipitates are collected by filtration, washed with water and dried to give 2 - cyclopropylmethyl - amino - 5 - chlorobenzophenone having a melting point of 82°—83°C. This product is identified with the compound obtained in Example 1 by means of its infrared absorption spectrum.

Example 4

A solution of 70 g. of chromic anhydride in 70 ml. of water is added dropwise to a suspension of 73.6 g. of 1 - cyclopropylmethyl - 2 - cyano - 3 - phenyl - 5 - chloroindole in 500 ml. of glacial acetic acid at room temperature. The mixture is stirred at room temperature overnight. The reaction mixture is then filtered, and the filtrate is poured into water and extracted with chloroform. The chloroform extracts are combined, washed with water and dried over sodium sulfate, and the solvent is removed under reduced pressure to give 55 g. of 2 - (N - cyclopropylmethylcyanocarbonylamino) - 5 - chlorobenzophenone as an oil.

To a solution of 34 g. of 2 - (N - cyclopropylmethyl - cyanocarbonylamino) - 5 -

chloro - benzophenone in 100 ml. of ethanol is added a solution of 120 g. of sodium hydroxide in 300 ml. of water, and the mixture is heated under reflux for 1 hour. The reaction mixture is extracted with chloroform. The chloroform extracts are combined, washed with water and dried over sodium sulfate, and the solvent is removed under reduced pressure. The residue is chromatographed on silica gel and eluted with chloroform to give 2 - cyclopropylmethylamino - 5 - chlorobenzophenone, mp. 82°—83°C. This product is identified with the compound obtained in Example 1 by means of its infrared absorption spectrum.

Example 5

To a solution of 11.4 g. of crude 2 - cyclopropylmethyl - amino - 5 - chlorobenzophenone in 100 ml. of glacial acetic acid is added 3.17 g. of potassium cyanate. The mixture is heated at 55°—60°C. with stirring overnight. The reaction mixture is poured into 500 ml. of ice-water. The precipitates are collected by filtration, washed with water and then with ether and dried to give 1 - cyclopropylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, mp. 169°—170°C.

The following compounds are produced in a manner similar to that of Example 5.

1 - Cyclopropylmethyl - 4 - phenyl - 6 - bromo - 2(1H) - quinazolinone, mp. 163°—164°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6 - fluoro - 2(1H) - quinazolinone, mp. 168.5°—169.5°C.

1 - Cyclopropylmethyl - 4 - phenyl - 2(1H) - quinazolinone, mp. 154°—155°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6 - nitro - 2(1H) - quinazolinone, mp. 172—173°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6 - methoxy - 2(1H) - quinazolinone, mp. 115°—116°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6 - methyl - 2(1H) - quinazolinone, mp. 162°—163°C.

1 - Cyclopropylmethyl - 4 - (*o* - fluorophenyl) - 6 - chloro - 2(1H) - quinazolinone, mp. 168°—169°C.

1 - Cyclopropylmethyl - 4 - (*o* - chlorophenyl) - 6 - chloro - 2(1H) - quinazolinone, mp. 202°—203°C.

1 - Cyclopropylmethyl - 4 - (*p* - methylphenyl) - 2(1H) - quinazolinone, mp. 159°—160°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6,7 - dichloro - 2(1H) - quinazolinone, mp. 206°—207°C.

1 - Cyclobutylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, mp. 115°—116°C.

1 - Cyclopentylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, mp. 222°—223°C.

1 - Cyclohexylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, mp. 224.5°—225.5°C.

1 - Cyclohexyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, mp. about 120°C.

1 - Cyclopropylmethyl - 4 - (2' - pyridyl) - 6 - bromo - 2(1H) - quinazolinone, mp. 121°—123°C (decomposition).

Example 6

To a solution of 2.86 g. of 2 - cyclopropylmethylamino - 5 - chlorobenzophenone in 20 ml. of glacial acetic acid is added 1.0 g. of sodium thiocyanate. The mixture is heated at 60°C. with stirring for 20 hours. After cooling, the reaction mixture is diluted with 50 ml. of chloroform and the mixture is washed three times with water. The organic layer is separated, dried over sodium sulfate and concentrated to dryness under reduced pressure. The oily residue is chromatographed on silica gel and eluted with chloroform to give 1 - cyclopropylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinethione. Recrystallization from a mixture of ethanol and chloroform gives orange needles, mp. 230°—231°C.

Example 7

To a solution of 5.72 g. of 2 - cyclopropylmethylamino - 5 - chlorobenzophenone in 40 ml. of glacial acetic acid is added 2.43 g. of potassium thiocyanate. The mixture is heated at 55°C. for 20 hours. Then, using a procedure similar to that described in Example 6, 1 - cyclopropylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinethione is obtained as orange crystals, mp. 225°—227°C.

Example 8

To a solution of 17.5 g. of ethyl 1 - (β - cyclohexylethyl) - 3 - phenyl - 5 - chloroindole - 2 - carboxylate in 95 ml. of glacial acetic acid is added dropwise a solution of 11.5 g. of chromic anhydride in 11.5 ml. of water at 20°—25°C. The mixture is stirred at room temperature for 30 minutes and heated at 50°—55°C. for 5 hours. After cooling, the reaction mixture is poured into 500 ml. of water and extracted with chloroform. The extracts are combined, washed with water and dried over sodium sulfate, and the solvent is removed under reduced pressure to give 17.5 g. of 2 - [N - (β - cyclohexylethyl) - ethoxalylamino] - 5 - chlorobenzophenone as an oil.

To a solution of 17.5 g. of the 2 - [N - (β - cyclohexylethyl) - ethoxyalylamino] - 5 - chlorobenzophenone thus obtained in 400 ml. of ethanol is added dropwise 150 ml. of concentrated hydrochloric acid, and the mixture

is refluxed for 7 hours. The solvent is then removed under reduced pressure. To the residue is added 300 ml. of cold water and the mixture is neutralized with concentrated ammonium hydroxide, and extracted with ether. The extracts are combined, washed with water and dried over sodium sulfate, and the solvent is removed under reduced pressure to give 10.7 g. of 2 - (β - cyclohexylethylamino) - 5 - chlorobenzophenone as a brown oil.

Example 9

To a solution of 6.84 g. of 2 - (β - cyclohexylethylamino) - 5 - chlorobenzophenone in 40 ml. of glacial acetic acid is added 1.8 g. of potassium cyanate. The mixture is heated at 53°—55°C. with stirring for 17 hours. After cooling, the reaction mixture is poured into 200 ml. of water, and then extracted with methylenedichloride. The organic layer is washed with water and dried over sodium sulfate, and the solvent is removed under reduced pressure. The residue is chromatographed on silica gel and is eluted with chloroform to give 3.46 g. of 1 - (β - cyclohexylethyl) - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone. Recrystallization from ethanol gives fine light yellow crystals, m.p. 115.5°—116.5°C.

Example 10

A solution of 13.5 g. of chromic anhydride in 13.5 ml. of water is added to a solution of 17.4 g. of ethyl 1 - cyclopropylmethyl - 3 - phenyl - 5 - trifluoromethylindole - 2 - carboxylate in 100 ml. of glacial acetic acid at 20°—25°C. The mixture is stirred at room temperature for 30 minutes, and heated at 50°—55°C. for 7 hours. After cooling, the reaction mixture is poured into 500 ml. of water and extracted with two 150 ml. portions of chloroform. The combined extracts are washed with water, dried over sodium sulfate, and concentrated in vacuo to dryness to give 16.4 g. of 2 - (N - cyclopropylmethylethoxalylamino) - 5 - trifluoromethylbenzophenone as an oil.

The 2 - (N - cyclopropylmethylethoxalylamino) - 5 - trifluoromethylbenzophenone thus obtained is dissolved in 200 ml. of 20% aqueous potassium hydroxide solution. The mixture is stirred and heated at 70°—80°C. for 4 hours, and then cooled in an ice bath. The yellow precipitates are collected by filtration, washed with water, and dried to give 7.47 g. of 2 - cyclopropylmethylamino - 5 - trifluoromethylbenzophenone, m.p. 102.0°—103.5°C.

Example 11

A mixture of 2.15 g. of 2 - cyclohexylamino - 5 - chlorobenzophenone, 3 g. of ethyl carbamate and 0.15 g. of zinc chloride is heated at 190°—200°C. (oil bath temperature) for 3 hours. After cooling, the reaction mixture is extracted with methylene chloride. The methylene chloride extracts are combined, washed with water, dried over sodium sulfate and concentrated to dryness under reduced pressure. The residue is chromatographed on silica gel and is eluted with benzene to give 1 - cyclohexyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone as a yellow solid, melting at about 120°C.

Infrared absorption spectrum (μ_{nujol}): 1600, 1590, 1580, 1540 cm^{-1}.

Using a procedure similar to that described above, 1 - cyclopropylmethyl - 4 - phenyl - 6 - trifluoromethyl - 2(1H) - quinazolinone is obtained mp. 166.5°—167.5°C.

Example 12

To a solution of 2.85 g. of 2 - cyclopropylmethylamino - 5 - chlorobenzophenonimine and 12 ml. of triethylamine in 70 ml. of benzene is added dropwise with cooling 70 ml. of a 10% phosgene solution in benzene. The mixture is stirred at room temperature for 30 minutes and then concentrated in vacuo to dryness.

To the residue are added 100 ml. of diluted aqueous sodium carbonate solution and 100 ml. of chloroform and the mixture is stirred. The aqueous layer is extracted with chloroform, and the organic layers are combined, washed with water and dried over sodium sulfate. The solvent is removed under reduced pressure and the residue is recrystallized from ethanol to give 1 - cyclopropylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, m.p. 171°—172°C.

Example 13

To a solution of 3.8 g. of 2 - cyclopropylmethylamino - 5 - chlorobenzophenone in 40 ml. of dry ether is added 3.6 g. of trichloroacetylchloride. The mixture is heated under reflux for 3 hours. After cooling, the reaction mixture is washed with water and dried over sodium sulfate, and the solvent is removed under reduced pressure. The oily residue is chromatographed on silica gel, and is eluted with benzene to give 3 g. of 2 - (N - cyclopropylmethyltrichloroacetamido) - 5 - chlorobenzophenone as a pale yellow oil.

Infrared absorption spectrum, μ_{max} 1680 cm^{-1} (C=O).

The 2 - (N - cyclopropylmethyltrichloroacetamino) - 5 - chlorobenzophenone (2.2 g.) thus obtained is dissolved in 20 ml. of ethanol. To the solution is added 30 ml. of ethanolic ammonia. The mixture is allowed to stand at room temperature for 24 hours. The reaction mixture is concentrated to dryness under reduced pressure. The residue is triturated with ether to give 1 - cyclopropylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone. Recrystallization from ethanol

gives pale yellow crystals having a melting point of 171°—172°C.

Example 14

By a procedure similar to that described in Example 13, but replacing 2 - cyclopropylmethylamino - 5 - chlorobenzophene by 2 - cyclopropylmethylamino - 5 - trifluoromethylbenzophenone, the compound 1 - cyclopropylmethyl - 4 - phenyl - 6 - trifluoromethyl - 2(1H) - quinazolinone, mp. 166.5°—167.5°C., is obtained.

The following compounds are produced in a manner similar to that described in Example 13 or 14.

1 - Cyclopropylmethyl - 4 - phenyl - 2(1H) - quinazolinone, mp. 154°—155°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6 - bromo - 2(1H) - quinazolinone, mp. 163°—164°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6 - fluoro - 2(1H) - quinazoline, mp. 168.5°—169.5°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6 - methyl - 2(1H) - quinazoline, mp. 162°—163°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6 - methoxy - 2(1H) - quinazolinone, mp. 115°—116°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6 - nitro - 2(1H) - quinazolinone, mp. 172°—173°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6,7 - dichloro - 2(1H) - quinazolinone, mp. 206°—207°C.

1 - Cyclopropylmethyl - 4 - phenyl - 6,8 - dichloro - 2(1H) - quinazolinone, mp. 158°—159°C.

1 - Cyclopropylmethyl - 4 - (*o* - fluorophenyl) - 6 - chloro - 2(1H) - quinazolinone, mp. 168°—169°C.

1 - Cyclopropylmethyl - 4 - (*o* - chlorophenyl) - 6 - chloro - 2(1H) - quinazolinone, mp. 202°—203°C.

1 - Cyclopropylmethyl - 4 - (*p* - tolyl) - 6 - chloro - 2(1H) - quinazolinone, mp. 159°—160°C.

1 - Cyclopropylmethyl - 4 - (2′ - pyridyl) - 6 - bromo - 2(1H) - quinazolinone, mp. 121°—123°C. (decomposition)

1 - Cyclobutylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, mp. 115°—116°C.

1 - Cyclopentylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, mp. 222°—223°C.

1 - Cyclohexylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, mp. 224.5°—225.5°C.

1 - Cyclohexylethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, mp. 115.5°—116.5°C.

1 - Cyclohexyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, mp. about 120°C.

Example 15

A solution of 5.13 g. of 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone in 100 ml. of dimethylformamide is added dropwise to a suspension of 1 g. of 50% sodium hydride in 30 ml. of dimethyl formamide. The mixture is stirred at 100°C. for 30 minutes. The mixture is cooled to room temperature and 5.4 g. of cyclopropylmethyl bromide are added dropwise thereto. The mixture is heated at 100°C. for 5 hours, with stirring. After cooling, the reaction mixture is poured into 300 ml. of water and extracted with chloroform. The chloroform extracts are combined, washed with dilute aqueous sodium hydroxide solution and filtered. The filtrate is washed with dilute hydrochloric acid, followed by water, and dried over sodium sulfate, and the solvent is removed under reduced pressure. The residue (7 g.) is chromatographed on silica gel, using chloroform as eluant. From the first fraction, 1.48 g. of 2 - cyclopropylmethoxy - 4 - phenyl - 6 - chloro - quinazoline is obtained as crystals having a melting point of 120°—121°C. From the second fraction 3.2 g. of 1 - cyclopropylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone is obtained as crystals having a melting point of 171°—172°C.

The 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone used as the starting material in this Example is obtained as follows:

To a stirred solution of 23.2 g. of 2 - amino - 5 - chlorobenzophenone and 10.1 g. of triethylamine in 100 ml. of dry ether is added dropwise a solution of 18.2 g. of trichloroacetylchloride in 30 ml. of dry ether with ice-cooling. The mixture is stirred for 2 hours at room temperature, and washed with water. The ether layer is dried over sodium sulfate, and concentrated in vacuo to dryness. The oily residue is crystallized from 50 ml. of ethanol to give 32.4 g. of 2 - trichloroacetamido - 5 - chlorobenzophenone as light yellow prisms, mp. 93.0°—94.0°C.

To a solution of 32.1 g. of 2 - trichloroacetamido - 5 - chlorobenzophenone in 600 ml. of dimethylsulfoxide are added 17.0 g. of triethylamine and 65.5 g. of ammonium acetate. The mixture is left at room temperature for 24 hours, and poured into 3 l of water. The precipitate is collected by filtration, washed with water and dried to give 21.4 g. of 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone, m.p. over 300°C.

Example 16

Using a procedure similar to that described in Example 15, but replacing 5.13 g. of 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone in 100 ml. of dimethylformamide, 1 g. of 50% sodium hydride in 30 ml. of dimethyl-

formamide and 5.4 g. of cyclopropylmethyl bromide by 10.7 g. of 4 - phenyl - 6 - nitro - 2(1H) - quinazolinone and 2.0 g. of 50% sodium hydride in 250 ml. of dimethylformamide and 12.0 g. of cyclopropylmethyl-bromide respectively, then 6.43 g. of 1 - cyclopropylmethyl - 4 - phenyl - 6 - nitro - 2(1H) - quinazolinone and 1.72 g. of 2 - cyclopropylmethoxy - 4 - phenyl - 6 - nitro - quinazoline are obtained.

The former is recrystallized from ethanol to give light yellow needles having a melting point of 172°—173°C. The latter is also recrystallized from ethanol to give colourless needles having a melting point of 142.0°—144.0°C.

The 4 - phenyl - 6 - nitro - 2(1H) - quinazolinone used as the starting material in this example is prepared as follows:

To a mixture of 12.1 g. of 2 - amino - 5 - nitrobenzophenone, 120 ml. of methylene chloride and 10 ml. of pyridine is added dropwise 10.9 g. of trichloroacetyl chloride at room temperature. The mixture is then stirred for 2 hrs., and 50 ml. of water is added with stirring. The organic layer is treated using a procedure similar to that described in Example 15, and 15.1 g. of 2 - trichloroacetamido - 5 - nitrobenzophenone, mp. 116°—117.5°C., is obtained. Recrystallization from a mixture of ethanol and chloroform gives light brown crystals, mp. 118.0°—119.0°C.

A solution of 3.9 g. of 2 - trichloroacetamido - 5 - nitrobenzophenone in 100 ml. of tertiary - butyl alcohol is heated with 3.4 g. of 10% ethanolic ammonia at about 120°C. for 3 hours in a sealed tube. The mixture is then concentrated in vacuo to dryness. The residue is washed with methylene chloride, and dried to give 4 - phenyl - 6 - nitro - 2(1H) - quinazolinone.

Example 17

To a suspension of 4.52 g. of 4 - phenyl - 6 - bromo - 2(1H) - quinazolinone in 70 ml. of dimethylformamide is added 0.63 g. of 62.5% sodium hydride. The mixture is heated at 100°C. for 30 minutes. The mixture is cooled to room temperature and 4.5 g. of cyclopropylmethyl bromide is added thereto. The mixture is heated at 100°C. for 6 hours. After cooling, the reaction mixture is poured into 400 ml. of water, acidified with hydrochloric acid and extracted with chloroform. The chloroform extracts are washed successively with dilute hydrochloric acid, with dilute aqueous sodium hydroxide solution and with water, and dried over sodium sulfate. The solvent is removed under reduced pressure. The residue is treated using a procedure similar to that described in Example 15, and 1.58 g. of 2 - cyclopropylmethoxy - 4 - phenyl - 6 - bromo - 2(1H) - quinazoline are obtained as crystals, which are recrystallized from ethanol to give colourless needles having a melting point of 133°—134°C., and 2.63 g. of 1 - cyclopropylmethyl - 4 - phenyl - 6 - bromo - 2(1H) - quinazolinone as crystals, which are recrystallized from ethanol to give fine pale yellow needles having a melting point of 163°—164°C.

The 4 - phenyl - 6 - bromo - 2(1H) - quinazolinone used as a starting material in this example is obtained using a procedure similar to that described in Examples 15 and 16. Recrystallization from ethanol - dimethylformamide gives crystals melting at 278°—280°C.

Example 18

Using a procedure similar to that described in Example 17, 3.6 g. of 4 - phenyl - 6 - fluoro - 2(1H) - quinazolinone and 5.4 g. of cyclopropylmethyl bromide are reacted to give 1.68 g. of 1 - cyclopropylmethyl - 4 - phenyl - 6 - fluoro - 2(1H) - quinazolinone and 1.0 g. of 2 - cyclopropylmethoxy - 4 - phenyl - 6 - fluoro - quinazoline. The former is recrystallized from ethanol to give pale yellow needles having a melting point of 168.5°—169.5°C. The latter is recrystallized from ethanol to give colourless crystals having a melting point of 92°—93°C.

The 4 - phenyl - 6 - fluoro - 2(1H) - quinazolinone used as the starting material in this example is obtained using to a procedure similar to that described in Examples 15 and 16.

Example 19

Using a procedure similar to that described in Example 17, but replacing 4 - phenyl - 6 - bromo - 2(1H) - quinazolinone by 3.78 g. of 4 - phenyl - 6 - methoxy - 2(1H) - quinazolinone, then 2.50 g. of 1 - cyclopropylmethyl - 4 - phenyl - 6 - methoxy - 2(1H) - quinazolinone as a brown oil and 1.64 g. of 2 - cyclopropylmethoxy - 4 - phenyl - 6 - methoxy - quinazoline as a yellow oil are obtained. The former is crystallized from a mixture of isopropyl ether and ethanol to give yellow prisms having a melting point of 115.0°—116.0°C.

The latter is crystallized from isopropyl ether to give light yellow needles having a melting point of 121.0°—122.0°C.

The 4 - phenyl - 6 - methoxy - 2(1H) - quinazolinone is synthesized by a procedure similar to that described in Example 15 and 16.

Example 20

A procedure similar to that described in Example 17 is carried out, but 4.52 g. of 4 - phenyl - 6 - bromo - 2(1H) - quinazolinone in 70 ml. of dimethylformamide, 0.63 g. of 62.5% sodium hydride and 4.5 g. of cyclopropylmethyl bromide are replaced by 5.49 g. of 4 - (*o* - fluorophenyl) - 6 - chloro -

2(1H) - quinazolinone in 100 ml. of dimethylformamide, 1 g. of 50% sodium hydride and 6 g. of cyclopropylmethyl bromide respectively. The reaction produces 1.48 g. of 2 - cyclopropylmethoxy - 4 - (*o* - fluorophenyl) - 6 - chloro - quinazoline as crystals, which are recrystallized from ethanol - chloroform (5 : 2) to give colourless needles having a melting point of 168°—169°C., and 1.85 g. of 1 - cyclopropylmethyl - 4 - (*o* - fluorophenyl) - 6 - chloro - 2(1H) - quinazolinone, which are recrystallized from ethanol to give pale yellow needles having a melting point of 171°—172°C.

Example 21

Using a procedure similar to that described in Example 20, but replacing 4 - (*o* - fluorophenyl) - 6 - chloro - 2(1H) - quinazolinone by 5.82 g. of 4 - (*o* - chlorophenyl) - 6 - chloro - 2(1H) - quinazolinone, then 3.51 g. of 1 - cyclopropylmethyl - 4 - (*o* - chlorophenyl) - 6 - chloro - 2(1H) - quinazolinone and 2.01 g. of 2 - cyclopropylmethoxy - 4 - (*o* - chlorophenyl) - 6 - chloro - quinazoline are obtained. Each of them is recrystallized from ethanol to give colourless needles having a melting point of 202.0°—203.0°C. for the former, and 171.0°—172.0°C. for the latter.

The 4 - (*o* - chlorophenyl) - 6 - chloro - 2(1H) - quinazolinone used as a starting material in this example is synthesized by a procedure similar to that described in Examples 15 and 16.

Example 22

Using a procedure similar to that described in Example 20, but replacing 4 - (*o* - fluorophenyl) - 6 - chloro - 2(1H) - quinazolinone by 4.73 g. of 4 - (*p* - tolyl) - 2(1H) - quinazolinone, then 2.73 g. of 1 - cyclopropylmethyl - 4 - (*p* - tolyl) - 2(1H) - quinazolinone and 1.0 g. of 2 - cyclopropylmethoxy - 4 - (*p* - tolyl) - quinazoline are obtained. The former is recrystallized from ethanol to give colourless needles having a melting point of 159°—160°C. The latter is also recrystallized from ethanol to give colourless prisms having a melting point of 80°—81°C.

4 - (*p* - Tolyl) - 2(1H) - quinazolinone used as the starting material in this example, is synthesized by a procedure similar to that described in Example 15 or 16.

Example 23

Using a procedure similar to that described in Example 20, but replacing 4 - (*o* - fluorophenyl) - 6 - chloro - 2(1H) - quinazolinone by 4.45 g. of 4 - phenyl - 2(1H) - quinazolinone, then 2.30 g. of 1 - cyclopropylmethyl - 4 - phenyl - 2(1H) - quinazolinone and 1.20 g. of 2 - cyclopropylmethoxy - 4 - phenylquinazoline are obtained. The former is recrystallized from ethanol to give light yellow plates having a melting point of 154.0°—155.0°C. The latter is recrystallized from ethanol to give light yellow prisms having a melting point of 98.0°—99.0°C.

The 4 - phenyl - 2(1H) - quinazolinone, used as a starting material in this example, is synthesized by a procedure similar to that described in Example 15 or 16.

Example 24

To a suspension of 2.36 g. of 4 - phenyl - 6 - methyl - 2(1H) - quinazolinone in 50 ml. of dimethylformamide is added 0.42 g. of 62.5% sodium hydride in aliquots. The mixture is heated at 100°C. for 30 minutes with stirring, and cooled to room temperature. Cyclopropylmethylbromide (3.0 g.) is then added dropwise to the mixture. The resulting mixture is treated by a procedure similar to that described in Example 15 and 0.82 g. of 2 - cyclopropylmethoxy - 4 - phenyl - 6 - methyl - quinazoline are obtained as crystals, which are recrystallized from ethanol to give colourless needles melting at 162°—167°C, and 1.46 g. of 1 - cyclopropylmethyl - 4 - phenyl - 6 - methyl - 2(1H) - quinazolinone as crystals, which are recrystallized from ethanol to give colourless needles melting at 95°—96°C.

The 4 - phenyl - 6 - methyl - 2(1H) - quinazolinone, used as a starting material in this example, is obtained using to a procedure similar to that described in Example 15 or 16. Recrystallization from dimethylformamide gives crystals, melting at 282°—283°C.

Example 25

A procedure similar to that described in Example 15 is carried out, the 5.13 g. of 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone in 100 ml. of dimethylformamide, 1 g. of 50% sodium hydride in 30 ml. of dimethylformamide and 5.4 g. of cyclopropylmethyl bromide are replaced by 5.82 g. of 4 - phenyl - 6,7 - dichloro - 2(1H) - quinazlinone in 100 ml. of dimethylformamide, 0.84 g. of 62.5% sodium hydride and 6.0 g. of cyclopropylmethyl bromide respectively. The reaction produces 2.40 g. of 2 - cyclopropylmethoxy - 4 - phenyl - 6,7 - dichloroquinazoline as crystals, which are recrystallized from ethanol to give colourless needles melting at 102°—103°C., and 2.54 g. of 1 - cyclopropylmethyl - 4 - phenyl - 6,7 - dichloro - 2(1H) - quinazolinone as crystals, which are recrystallized from ethanol - chloroform to give pale yellow prisms melting at 206°—207°C.

Example 26

A procedure similar to that described in Example 17 is carried out, but the 4.52 g. of 4 - phenyl - 6 - bromo - 2(1H) - quinazolinone in 100 ml. of dimethylformamide, 0.84 g. of 62.5% sodium hydride and 4.5 g.

of cyclopropylmethyl bromide are replaced by 5.13 g. of 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone in 100 ml. of dimethylformamide, 0.84 g. of 62.5% sodium hydride and 6.0 g. of cyclobutylmethyl bromide respectively. The reaction produces 2.73 g. of 2 - cyclobutylmethoxy - 4 - phenyl - 6 - chloroquinazoline as a yellow oil and 1.87 g. of 1 - cyclobutylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone as crystals, which are recrystallized from ethanol to give pale yellow needles having a melting point of 115°—116°C.

Example 27

By a procedure similar to that described in Example 26, 5.13 g. of 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone is allowed to react with 7.1 g. of cyclohexylmethyl bromide to give the two isomers 1 - cyclohexylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone and colourless leaflets (from ethanol) melting at 224.5°—225.5°C. and 2 - cyclohexylmethoxy - 4 - phenyl - 6 - chloroquinazoline as colourless crystals melting at 87°—88°C.

Example 28

By a procedure similar to that described in Example 26, 5.13 g. of 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone is allowed to react with 6.52 g. of cyclopentylmethyl bromide to give the two isomers 1 - cyclopentylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone as pale yellow leaflets (from ethanol - chloroform) melting at 222°—223°C. and 2 - cyclopentylmethoxy - 4 - phenyl - 6 - chloro - quinazoline as yellow crystals melting at 82°—84°C.

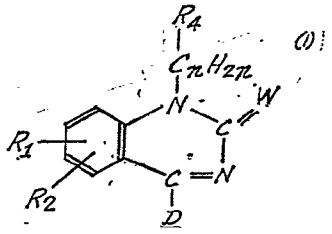
Example 29

Using a procedure similar to that described in Example 17, 1.21 g. of 4 - (2′ - pyridyl) - 6 - bromo - 2(1H) - quinazolinone in 20 ml. of dimethylformamide, 0.17 g. of 62.5% sodium hydride, and 1.2 g. of cyclopropylmethyl bromide are allowed to react. The reaction mixture is poured into 100 ml. of water and extracted with ether. The ethereal extracts are washed with water, dried over sodium sulfate and concentrated to dryness. The residue (0.87 g.) is chromatographed on silica gel. Elution with chloroform gives 2 - cyclopropylmethoxy - 4 - (2′ - pyridyl) - 6 - bromo - quinazoline, which is recrystallized from ethanol to give pale yellow needles melting at 108°—109°C.

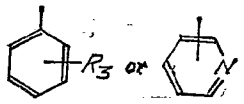
Further elution of the column with ethyl acetate yields 1 - cyclopropylmethyl - 4 - (2′ - pyridyl) - 6 - bromo - 2(1H) - quinazolinone as an oil, which is crystallized from ethanol - petroleum benzin. Recrystallization from ethanol - benzene gives 1 - cyclopropylmethyl - 4 - (2′ - pyridyl) - 6 - bromo - 2(1H) - quinazolinone monoethanolate as pale yellow prisms, mp. 121°—123°C. (decompositions).

WHAT WE CLAIM IS:—

1. A quinazoline derivative of the formula,



wherein D is a group of the formula,



W is an oxygen or sulfur atom; n is 0, 1, 2 or 3;; R_1, R_2 and R_3 are each independently a hydrogen or halogen atom, or a nitro, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfinyl or trifluoromethyl group; and R_4 is an unsubstituted or C_{1-4} alkyl - substituted C_{3-6} cycloalkyl group, or a pharmaceutically acceptable acid addition salt thereof.

2. A quinazoline derivative or a pharmaceutically acceptable acid addition salt thereof according to Claim 1, wherein n is 1 and R_4 is a cyclopropyl group.

3. A quinazoline derivative or a pharmaceutically acceptable acid addition salt thereof according to Claim 1, wherein D is a phenyl, o - halogenophenyl or 2 - pyridyl group; n is 1; R_1 is a hydrogen or halogen atom, or a methyl, methoxy, nitro or trifluoromethyl group, R_1 being substituted at the 6 - position of the quinazoline ring; R_2 is a hydrogen atom and R_4 is a cyclopropyl group.

4. A quinazoline derivative or a pharmaceutically acceptable acid addition salts thereof according to Claim 1, wherein D is a phenyl group; n is 1; W is oxygen; R_1 is a halogen atom or a nitro group, R_1 being substituted at the 6 - position of the quinazoline ring; R_2 is a hydrogen atom; and R_4 is a cyclopropyl group.

5. 1 - Cyclopropylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinone or a pharmaceutically acceptable acid addition salt thereof.

6. 1 - Cyclopropylmethyl - 4 - phenyl - 6 - nitro - 2(1H) - quinazolinone or a pharmaceutically acceptable acid addition salt thereof.

7. 1 - Cyclopropylmethyl - 4 - phenyl - 2(1H) - quinazolinone or a pharmaceutically acceptable acid addition salt thereof.

8. 1 - Cyclopropylmethyl - 4 - phenyl - 6 - fluoro - 2(1H) - quinazolinone or a

pharmaceutically acceptable acid addition salt thereof.

9. 1 - Cyclopropylmethyl - 4 - phenyl - 6 - bromo - 2(1H) - quinazolinone or a pharmaceutically acceptable acid addition salt thereof.

10. 1 - Cyclopropylmethyl - 4 - phenyl - 6 - methyl - 2(1H) - quinazolinone or a pharmaceutically acceptable acid addition salt thereof.

11. 1 - Cyclopropylmethyl - 4 - phenyl - 6 - methoxy - 2(1H) - quinazolinone or a pharmaceutically acceptable acid addition salt thereof.

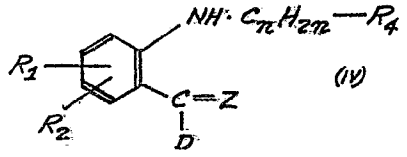
12. 1 - Cyclopropylmethyl - 4 - phenyl - 6 - trifluoromethyl - 2(1H) - quinazolinone or a pharmaceutically acceptable acid addition salt thereof.

13. 1 - Cyclopropylmethyl - 4 - (*o* - fluorophenyl) - 6 - chloro - 2(1H) - quinazolinone or a pharmaceutically acceptable acid addition salt thereof.

14. 1 - Cyclopropylmethyl - 4 - phenyl - 6 - chloro - 2(1H) - quinazolinethione or a pharmaceutically acceptable acid addition salt thereof.

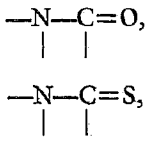
15. 1 - Cyclopropylmethyl - 4 - (2' - pyridyl) - 6 - bromo - 2(1H) - quinazolinone or a pharmaceutically acceptable acid addition salt thereof.

16. A process which includes reacting a compound of the formula,



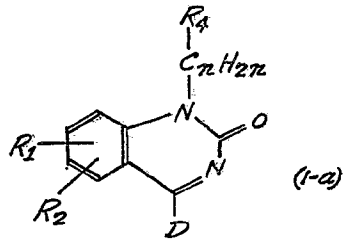
(IV)

wherein D, n, R_1, R_2 and R_4 are as defined in Claim 1; and Z is an oxygen atom or an imino group, with a compound containing a



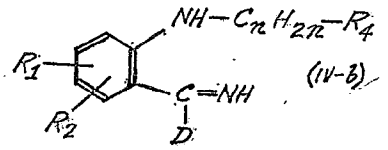
group in the molecule, to yield a quinazoline derivative of the formula (I) as claimed in Claim 1.

17. A process for preparing a quinazoline derivative of the formula,



(I-a)

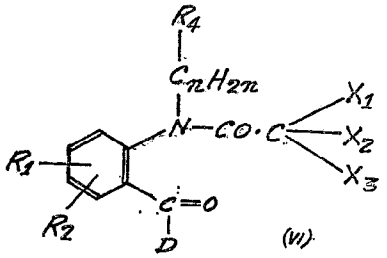
wherein D, n, R_1, R_2 and R_4 are as defined in Claim 1, which includes reacting a compound of the formula,



(IV-b)

wherein D, n, R_1, R_2 and R_4 are as defined in Claim 1, with phosgene to yield the said quinazoline derivative of the formula (I-a).

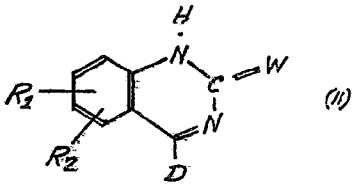
18. A process for producing a quinazoline derivative of the formula I-a given and defined in Claim 17 which includes reacting a trihalogenoacetamido derivative of the formula,



(VI)

wherein D, n, R_1, R_2 and R_4 are as defined in Claim 1, and X_1, X_2 and X_3 are each independently a halogen atom, with ammonia to yield the said quinazoline derivative of the formula (I-a).

19. A process which includes reacting a 1 - unsubstituted quinazoline derivative of the formula,



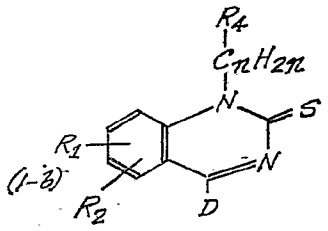
(II)

wherein D, R_1, R_2 and W are as defined in Claim 1, with a reactive derivative of a compound of the formula,

$$HO—C_nH_{2n}—R_4 \qquad (III)$$

wherein n and R_4 are as defined in Claim 1, to yield a quinazoline derivative of the formula given and defined in Claim 1.

20. A process for producing a quinazoline derivative of the formula,



(I-a)

wherein D, n, R_1, R_2 and R_4 are as defined in Claim 1 which includes reacting a derivative of the formula I-a, as given and defined in Claim 17, with phosphorus pentasulfide to yield the quinazoline derivative of the formula I-b.

21. A process for producing a quinazoline derivative of the formula I-a, given and defined in Claim 17, which includes reacting a quinazoline derivative of the formula (I-b), as given and defined in Claim 20, with an oxidising agent in a solvent or solvent mixture to yield the said quinazoline derivative of the formula (I-a).

22. A process according to Claim 16, wherein the compound containing a

$$—\overset{|}{N}—\overset{|}{C}=O,$$

or

$$N=C=O$$

group in the molecule is cyanic acid, sodium cyanate, potassium cyanate, ammonium cyanate, an alkyl carbamate or a carbamic acid halide.

23. A process according to Claim 16 wherein the compound containing a

$$—\overset{|}{N}—\overset{|}{C}=S,$$

or

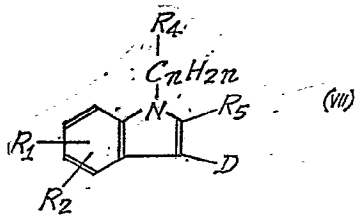
$$—N=C=S$$

group in the molecule is thiocyanic acid, sodium thiocyanate, potassium thiocyanate or ammonium thiocyanate.

24. A process according to Claim 19 wherein the reactive derivative of the compound of the formula (III) is a hydrohalic acid or sulfonic acid ester.

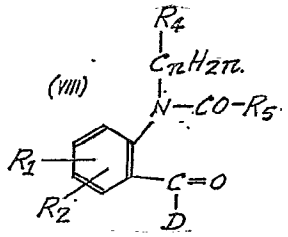
25. A process according to Claim 19 or 24, wherein the reaction of the 1 - unsubstituted quinazoline derivative of the formula (II) with the reactive derivative of the compound of the formula (III) is carried out either in the presence of an alkaline agent, or of a metal salt of the 1 - unsubstituted quinazoline derivative formed by reacting a derivative of the formula (II) with an alkaline agent.

26. A process according to Claim 16, 22 or 23, which includes the preliminary step of preparing the compound of the formula (IV) by reacting an indole derivative of the formula,



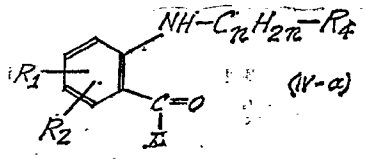
(VII)

wherein D, n, R_1, R_2 and R_4 are as defined in Claim 1; and R_5 is a C_{1-4} alkoxy - carbonyl, carboxy, carbamoyl or cyano group, with an oxidizing agent to yield a compound of the formula,



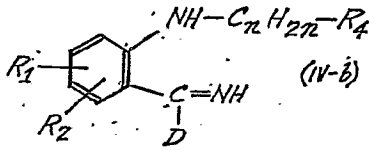
(VIII)

wherein D, n, R_1, R_2, R_4 and R_5 are as defined above, hydrolyzing the compound of the formula (VIII) to yield a compound of the formula,



(IV-a)

wherein D, n, R_1, R_2 and R_4 are as defined above, and thereafter, optionally reacting the resultant compound of the formula (IV-a) with ammonia to yield a compound of the formula,

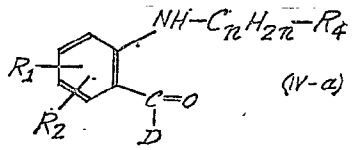


(IV-b)

wherein D, n, R_1, R_2 and R_4 are as defined above.

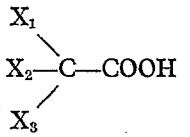
27. A process according to Claim 26, wherein the oxidizing agent is ozone, hydrogen peroxide, performic acid, peracetic acid, perbenzoic acid, chromic acid or potassium permanganate.

28. A process according to Claim 18, which includes the preliminary step of preparing the trihalogenoacetamido derivative of the formula (VI) by reacting a compound represented by the formula,



(IV-a)

wherein D, n, R_1, R_2 and R_4 are as defined in Claim 1, with a trihalogenoacetic acid represented by the formula,

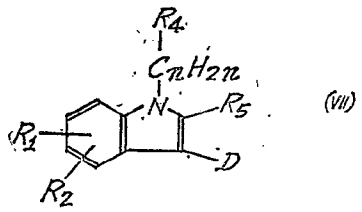


(V)

wherein X_1, X_2 and X_3 are each independently a halogen atom, or a reactive derivative thereof.

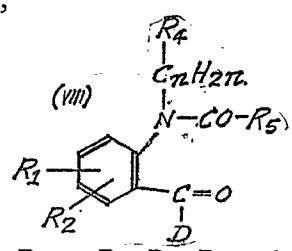
29. A process according to Claim 28, wherein the reactive derivative of the trihalogenoacetic acid is an acid halide, anhydride or ester.

30. A process according to Claim 16, 22, 23, or 28, which includes the preliminary step of preparing a compound of the formula (IV-a) by reacting an indole derivative of the formula,



(VII)

wherein D, n, R_1, R_2 and R_4 are as defined in Claim 1; and R_5 is a C_{1-4} alkoxy - carbonyl, carboxy, carbamoyl or cyano group, with an oxidizing agent to yield a compound of the formula,

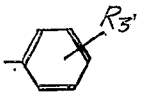


(VIII)

wherein D, n, R_1, R_2, R_4 and R_5 are as defined above, and hydrolyzing the said compound of the formula (VIII) thus obtained.

31. A pharmaceutical composition containing as an active ingredient a quinazoline derivative or a pharmaceutically acceptable acid addition salt thereof as claimed in claim 1, and a pharmaceutically acceptable carrier.

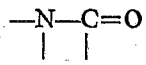
32. A process according to claim 16, for preparing a quinazoline derivative within the formula (I), given and defined in claim 1, in which formula R_1 is a hydrogen or halogen atom, or a nitro, trifluoromethyl, C_{1-4} alkoxy, C_{1-4} alkylthio or C_{1-4} alkylsulfonyl group; R_2 is a hydrogen atom; D is a group of the formula,



(wherein R_3 is a hydrogen or halogen atom, or a C_{1-4} alkyl, C_{1-4} alkoxy or trifluoromethyl group); W is an oxygen atom; and wherein the compound containing a

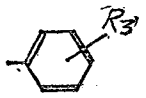
$$-N=C=O$$

or



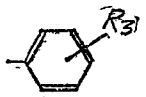
group in the molecule is cyanic acid or a salt thereof, or a carbamic acid ester.

33. A process according to claim 18 for preparing a quinazoline derivative with the formula (I-a), given and defined in claim 17, in which formula D is a group of the formula,



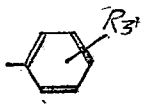
and R_1, R_2 and R_3 are each independently a hydrogen or halogen atom, or a C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfonyl, nitro or trifluoromethyl group; and n is 1, 2 or 3.

34. A process according to claim 28 for preparing a quinazoline derivative within the formula (I-a), given and defined in claim 17, in which formula D is a group of the formula,



and R_1, R_2 and R_3 are each independently a hydrogen or halogen atom, or a nitro, trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio or C_{1-4} alkylsulfonyl group; and n is 1, 2 or 3.

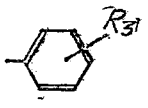
35. A process according to claim 30 for preparing a quinazoline derivative within the formula (I-a), given and defined in claim 17, in which formula R_1 is a hydrogen or halogen atom or a nitro group; R_2 is a hydrogen atom; D is a group of the formula,



(wherein R_3 is a hydrogen or halogen atom); R_4 is an unsubstituted or C_{1-4} alkyl - substituted C_{3-6} cyclo - alkyl group; and n is 1, 2 or 3; the oxidation of the indole derivative within the formula (VII) to the compound within the formula (VIII) being optionally effected in the presence of water.

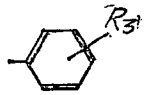
36. A process according to claim 35 for preparing a quinazoline derivative within the formula (I-a), given and defined in claim 17, in which formula n is additionally zero.

37. A process according to claim 30 for preparing a quinazoline derivative of the formula (I-a), given and defined in claim 17, in which formula R_1 is a hydrogen or halogen atom or a nitro group; R_2 is a hydrogen atom; R_4 is an unsubstituted or C_{1-4} alkyl - substituted C_{3-6} cyclo - alkyl group; n is 1, 2 or 3; and D is a group of the formula



(wherein R_3 is a hydrogen or halogen atom), and wherein the resultant compound of the formula (IV-a) is reacted with cyanic acid or a salt thereof or carbamic acid halide or a carbamic acid ester to obtain a quinazoline derivative within the formula (I-a).

38. A process according to claim 19 for preparing a quinazoline derivative within the formula (I), given and defined in claim 1, in which formula R_1 is a hydrogen or halogen atom, or a nitro, trifluoromethyl, C_{1-4} alkoxy, C_{1-4} alkylthio or C_{1-4} alkylsulfonyl group; R_2 is a hydrogen atom; D is a group of the formula,



(wherein R_3 is a hydrogen or halogen atom, or a C_{1-4} alkyl, C_{1-4} alkoxy or trifluoromethyl group), and W is an oxygen atom.

39. Quinazoline derivatives as defined in claim 1 which are specifically disclosed herein.

40. Processes for producing quinazoline derivatives as defined in claim 1 substantially as herein described and exemplified.

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